ADVAGRAF® PROLONGED-RELEASE HARD CAPSULES

Tacrolimus (0.5 mg, 1 mg, 5 mg)

What is in this leaflet

What *Advagraf* is used for

Following your organ transplant (liver, kidney), Advagraf is used to control your body's immune response, enabling your body to accept the transplanted organ.

You may also be given Advagraf for an ongoing rejection of your transplanted liver or kidney, when any previous treatment you were taking was unable to control this immune response after your transplantation.

Advagraf is used in adults.

How *Advagraf* works

Advagraf contains an active ingredient called tacrolimus. It belongs to a group of medicines called immunosuppressants. Advagraf reduces your body's own defense mechanism to stop you rejecting your transplanted organ.

Before you use *Advagraf*

- When you must not use it

If you are allergic (hypersensitive) to:
- tacrolimus or any of the other ingredients of Advagraf.
- macrolide antibiotics (e.g. *erythromycin, clarithromycin, josamycin).*

- Before you start to use it

Talk to your doctor or pharmacist before taking Advagraf.
- If you have liver problems or have had a disease which may have affected your liver, please tell your doctor as this may affect the dose of Advagraf that you receive.
- If you have an alteration of the electrical activity of your heart called QT prolongation.
- If you have diarrhoea for more than one day, please tell your doctor, because it might be necessary to adapt the dose of Advagraf that you receive.
- If you have or have had damage to the smallest blood vessels, known as thrombotic microangiopathy /thrombotic thrombocytopenic purpura/haemolytic uraemic syndrome. Tell your doctor if you develop fever, bruising under the skin (which may appear as red dots), unexplained tiredness, confusion, yellowing of the skin or eyes, reduced urine output, vision loss and seizures (see **Side effects**).
- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. One study assessed pregnancy outcomes in women treated with tacrolimus and those treated with other immunosuppressants. While there was insufficient evidence in this study to draw conclusions, higher rates of miscarriage were reported among liver and kidney transplant patients treated with tacrolimus, as well as higher rates among kidney transplant patients of persistent hypertension associated with protein loss in the urine that develops during pregnancy or the postpartum period (a condition called pre-eclampsia). No increased risk of major birth defects associated with Advagraf use was found. Advagraf passes into breast milk. Therefore, you should not breast-feed whilst using Advagraf.

Advagraf contains lactose (milk sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking Advagraf.

The printing ink used on Advagraf capsules contains soya lecithin.
If you are allergic to peanut or soya, talk to your doctor to determine whether you should use this medicine.

- Precaution for handling:

Direct contact with any part of your body like your skin or eyes, or breathing in powder contained in tacrolimus products should be avoided during preparation. If such contact occurs, wash the skin and eyes.

- Children and adolescents

The use of Advagraf is not recommended in children and adolescents under 18 years.

- Taking other medicines

Tell your doctor if you are taking any other medicines, including any that you buy without a prescription from a pharmacy, supermarket or health food shop.

Advagraf must not be taken with ciclosporin.

If you need to attend a doctor other than your transplant specialist, tell the doctor that you are taking tacrolimus.

Your doctor may need to consult your transplant specialist if you should use another medicine that could increase or decrease your tacrolimus blood level.

Other medicines you take can affect Advagraf blood levels, and Advagraf can affect blood levels of other medicines, which may require interruption, an increase or a decrease in Advagraf dose.

As increased tacrolimus blood levels could lead to serious side effects (see **Side effects**), frequent continued monitoring of your Advagraf blood level may be needed within the first few days of starting another medicine

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and during treatment with the other medicine. Some other medicines may cause tacrolimus blood levels to decrease, which could increase the risk of rejecting the transplanted organ.

Tell your doctor if you are taking or have recently taken medicines with active substances like:
- antifungal medicines e.g. ketoconazole, fluconazole, itraconazole, posaconazole, voriconazole, clotrimazole, isavuconazole, miconazole, caspofungin
- antibiotics, particularly so-called macrolide antibiotics, used to treat infections e.g. telithromycin, erythromycin, clarithromycin, josamycin, azithromycin, rifampicin, rifabutin, isoniazid, and flucloxacillin
- letermovir, used to prevent illness caused by CMV (human cytomegalovirus)
- ritonavir, nelfinavir, saquinavir, efavirenz, etravirine, nevirapine used to treat HIV infection
- telaprevir, boceprevir, the combination ombitasvir/paritaprevir/ritonavir with or without dasabuvir, elbasvir/grazoprevir, and glecaprevir/pibrentasvir), used to treat hepatitis C infection
- nilotinib and imatinib, idelalisib, ceritinib, crizotinib, apalutamide, enzalutamide, or mitotane (used to treat certain cancers)
- mycophenolic acid, used to suppress the immune system to prevent transplant rejection
- medicines for stomach ulcer and acid reflux (e.g. omeprazole, lansoprazole or cimetidine)
- antiemetics, used to treat nausea and vomiting (e.g. metoclopramide)
- the antacid magnesium-aluminium-hydroxide, used to treat heartburn
- the contraceptive pill or other hormone treatments with ethinylestradiol, hormone treatments with danazol
- medicines used to treat high blood pressure or heart problems (e.g. nifedipine, nicardipine, diltiazem and verapamil)
- amiodarone used to control arrhythmia (uneven beating of the heart)
- carbamazepine, phenytoin or phenobarbital, used to treat epilepsy
- metamizole, used to treat pain and fever
- the corticosteroids including prednisolone and methylprednisolone, used to treat inflammations or suppress the immune system (e.g. in transplant rejection)
- nefazodone, used to treat depression
- herbal preparations containing St. John's wort (*Hypericum perforatum*) or extracts of *Schisandra sphenanthera*
- cannabidiol (uses amongst others include treatment of seizures).

Tell your doctor if you are taking sirolimus or everolimus. When tacrolimus is taken together with sirolimus or everolimus, the risk of developing thrombotic microangiopathy, thrombotic thrombocytopenic purpura, and haemolytic uraemic syndrome may increase (see **Side effects**).

Food and drink
Grapefruit and grapefruit juice should be avoided while using Advagraf.

How to use *Advagraf*
- How much to use
Follow all directions given to you by your doctor and pharmacist carefully. They may differ from the information contained in this leaflet. If you do not understand the instructions on the label, ask your doctor or pharmacist for help.
Make sure that you receive the same tacrolimus medicine every time you collect your prescription, unless your transplant specialist has agreed to change to a different tacrolimus medicine.

Initial oral doses just after transplantation will generally be in the range of 0.1–0.3 mg per kg body weight per day, depending on the transplanted organ.

Your dose depends on your general condition and on which other immunosuppressive medication you are taking. Regular blood tests by your doctor will be required to define the correct dose and to adjust the dose from time to time. Your doctor will usually reduce your Advagraf dose once your condition has stabilised. Your doctor will tell you exactly how many capsules to take and how often. The capsules should be swallowed whole with a glass of water.

- *When to use it*
Advagraf capsule is taken orally once daily in the morning. You should generally take Advagraf on an empty stomach or at least 1 hour before or 2 to 3 hours after the meal.
Use as directed by your doctor or pharmacist.

- *How long to use it*
Take Advagraf for time period set by your doctor.

- If you forget to use it
Consult your doctor or pharmacist on what you should do if you forget to use it.
Take the missed dose as soon as you remember. If it is almost time for your next dose, wait until then to take the medicine and skip the missed dose. Do not take a double dose to make up for the missed dose on the next morning.

- If you use too much (overdose)
Contact your doctor immediately or go to the Emergency Department of your nearest hospital, if you think you or anyone else may have taken too much of this medicine. Do this even if there are no signs of discomfort or

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poisoning. You may need urgent medical attention.

Taking too many capsules may cause tremor, headache, nausea and vomiting, infections, hives, lethargy, increase in blood levels of urea and creatinine (urea and creatinine are waste products of the body), and increase in alanine aminotransferase levels (liver enzyme).

While you are using it

- Things you must do

- Tell all the doctors, dentists and pharmacists treating you that you are taking Advagraf.
- Tell your doctor immediately if you become pregnant while taking this medication.
- Attend all the appointments given to you as your doctor may carry out a number of tests from time to time. This is important and will help your doctor to decide on the most appropriate dose of Advagraf for you.
- Limit your exposure to sunlight and UV light whilst taking Advagraf by wearing appropriate protective clothing and using a sunscreen with a high sun protection factor. This is because of the potential risk of malignant skin changes with immunosuppressive therapy.
- If you need to have any vaccinations, please inform your doctor beforehand. Your doctor will advise you on the best course of action.
- Patients treated with Advagraf have been reported to have an increased risk of developing lymphoproliferative disorders and other malignancies, including skin cancers and Kaposi's sarcoma. Ask your doctor for specific advice on these disorders.

- Things you must not do

- Do not stop taking the medicine unless advised by your doctor. Stopping your treatment with Advagraf may increase the risk of rejection of your transplanted organ.
- Do not take any new medicines without consulting your doctor.
- Do not give Advagraf to anyone else, even if they have the same symptoms or condition as you.

- Things to be careful of

Driving and using machines

Do not drive or use any tools or machines if you feel dizzy or have a headache or problems seeing clearly after taking Advagraf. These effects are enhanced if you also drink alcohol.

Side effects

Like all medicines, Advagraf can cause side effects, although not everybody gets them.
Visit your doctor or pharmacist immediately if you experience any side effects after taking this medicine.

Since Advagraf reduces your body's defense mechanism (immune system) to fight infections, you may be more prone to infections while taking Advagraf.
Some infections caused by bacteria, viruses, fungi, or parasites could be serious or fatal.

Tell your doctor immediately if you notice any of the following as you may need urgent medical care:

- signs of allergy such as rash, itching or hives on the skin; swelling of the face, lips, tongue or other part of the body; shortness of breath, wheezing or troubled breathing
- fever
- diabetes / increased blood sugar
- swelling, numbness or tingling (pins and needles) in your hands and feet
- "flu-like" symptoms such as chills, sore throat, aching joints, swollen glands, or any other signs of infection
- unusual bleeding or bruising
- high blood pressure
- palpitations, abnormal heart rhythms, chest pain
- skin changes such as new or changing discoloration, lesions, lumps or moles, or changes to existing moles, anywhere on the body
- swelling of the eyelids, hands or feet due to excess fluid
- a change in the amount of urine passed or in the number of times you urinate, pain on urinating, or other kidney problems
- yellowing of the skin and/or eyes (jaundice) often accompanied by generally feeling unwell (for example, extreme tiredness, lack of energy, loss of appetite, nausea and vomiting, pain in the abdomen)
- symptoms of anaemia, such as shortness of breath, tiredness or dizziness, abnormal paleness of the skin, coldness in hands and feet
- vision loss and seizures (fits)
- buzzing or ringing in the ears, difficulty hearing
- erosion and blistering of skin or mucous membranes, red swollen skin that can detach in large parts of the body
- blindness
- confusion, mood changes, disorientation, nightmare, hallucination, mental disorders
- reductions in blood cell counts
- increase in white blood cell counts
- decreased/increased potassium in the blood
- liver function tests abnormal
- reduced magnesium, phosphate, calcium or sodium in the blood
- ulcers in the stomach or mouth, collection of fluid in the body
- strong abdominal pain accompanied or not with other symptoms, such as chills, fever, nausea or vomiting
- inflammation or bleeding in the stomach
- increased uric acid, acids, lipids, or alkaline phosphatase in the blood
- constipation, bloating, loose stools

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- hair loss, acne, increased sweating
- back pain
- weight gain or loss
- feeling of body temperature change

Other side effects not listed above may also occur in some people. Tell your doctor if you notice any other side effects.

You may report any side effects or adverse drug reactions directly to the National Centre for Adverse Drug Reaction Monitoring by visiting the website npra.gov.my
[Consumers → Reporting Side Effects to Medicines (ConSERF) or Vaccines (AEFI)].

Storage and Disposal of *Advagraf*
- Storage
Keep out of the reach and sight of children.
Do not store above 30°C. Store in the original package in order to protect from moisture.
After opening of the aluminium pouch, the capsules are stable for 12 months.

- Disposal
Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

Product Description
- What it looks like
Advagraf Capsules 0.5 mg, 1 mg and 5 mg are hard gelatin capsules containing white powder. It is supplied in blisters containing 10 capsules within a protective foil wrapper.
Advagraf 0.5 mg capsules
Imprinted in red with "0.5 mg" on the light yellow capsule cap and "647" on the orange capsule body.
Advagraf 1 mg capsules
Imprinted in red with "1 mg" on the white capsule cap and "677" on the orange capsule body.
Advagraf 5 mg capsules
Imprinted in red with "5 mg" on the greyish red capsule cap and "687" on the orange capsule body.

- Ingredients
- Active ingredient
Advagraf Capsule 0.5 mg contains 0.5 mg of tacrolimus.
Advagraf Capsule 1 mg contains 1 mg of tacrolimus.
Advagraf Capsule 5 mg contains 5 mg of tacrolimus.

- Inactive ingredients
This medicine contains less than 1 mmol sodium (23 mg) per capsule, that is to say essentially 'sodium-free'.
- Capsule content:
Hypromellose, ethylcellulose, lactose, magnesium stearate.
- Capsule shell:
Titanium dioxide (E 171), yellow iron oxide (E 172), red iron oxide (E172), sodium laurilsulfate, gelatine.
- Printing ink of capsule shell:
Shellac, lecithin (soya), hydroxypropyl cellulose, simeticone, red iron oxide (E172).

- *MAL number:*
Advagraf 0.5 mg capsules
MAL12115074AZ
Advagraf 1 mg capsules
MAL12115073AZ
Advagraf 5 mg capsules
MAL12115072AZ

Manufacturer
Astellas Ireland Co., Ltd.
Killorglin, Co. Kerry, V93 FC86,
Ireland

Product Registration Holder
Astellas Pharma Malaysia Sdn. Bhd.
Unit 9.02 and 9.03
Level 9, Corporate Tower 2,
Pavilion Damansara Heights,
3, Jalan Damanlela, Pusat Bandar Damansara,
50490 Kuala Lumpur.

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